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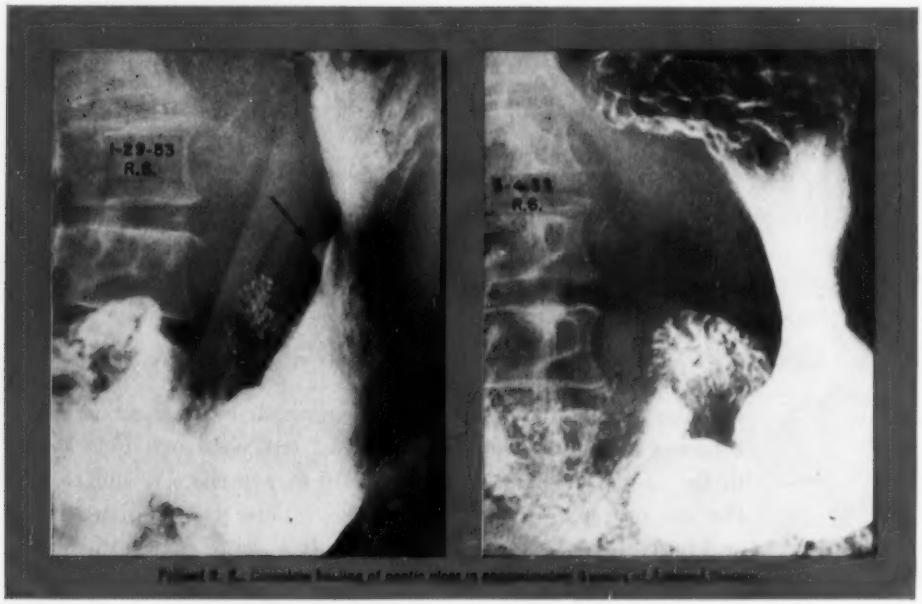

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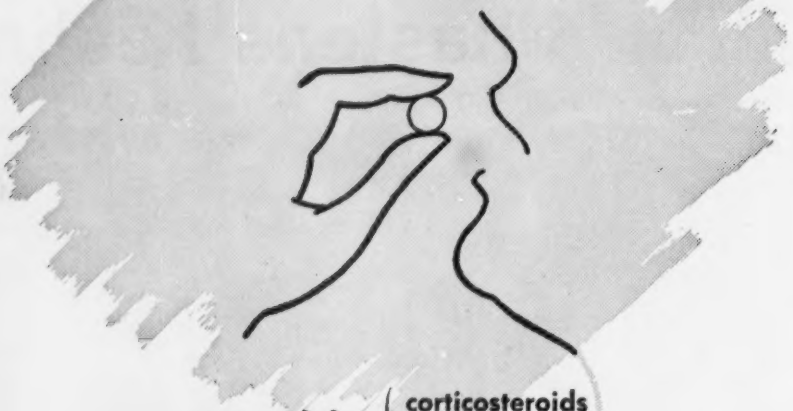

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July 1956

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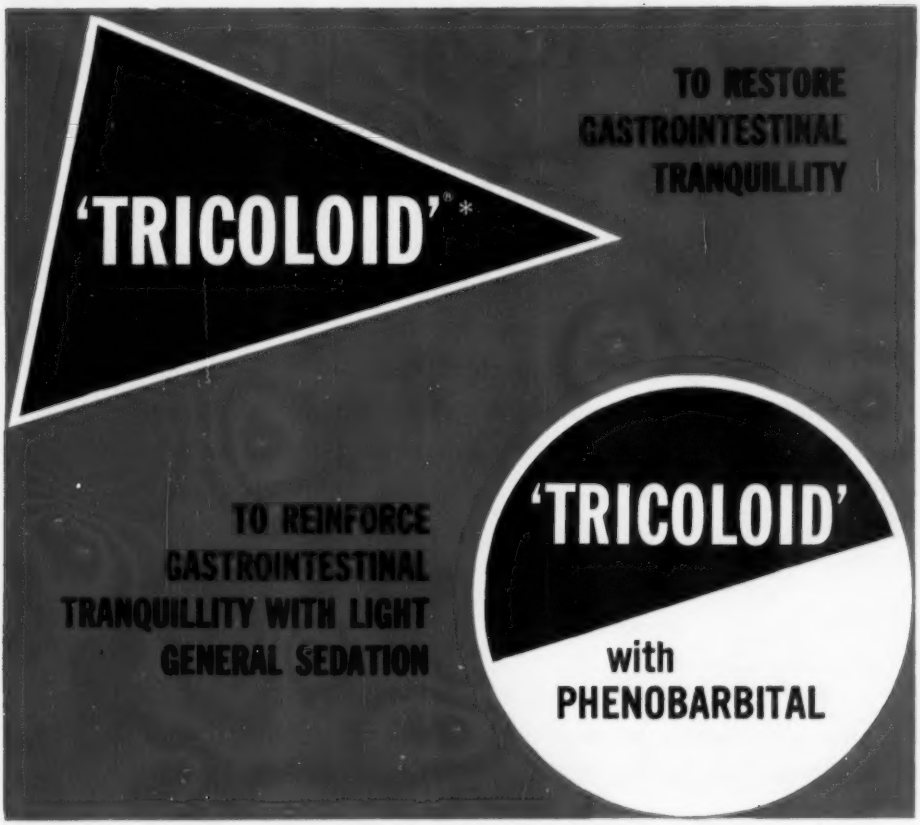

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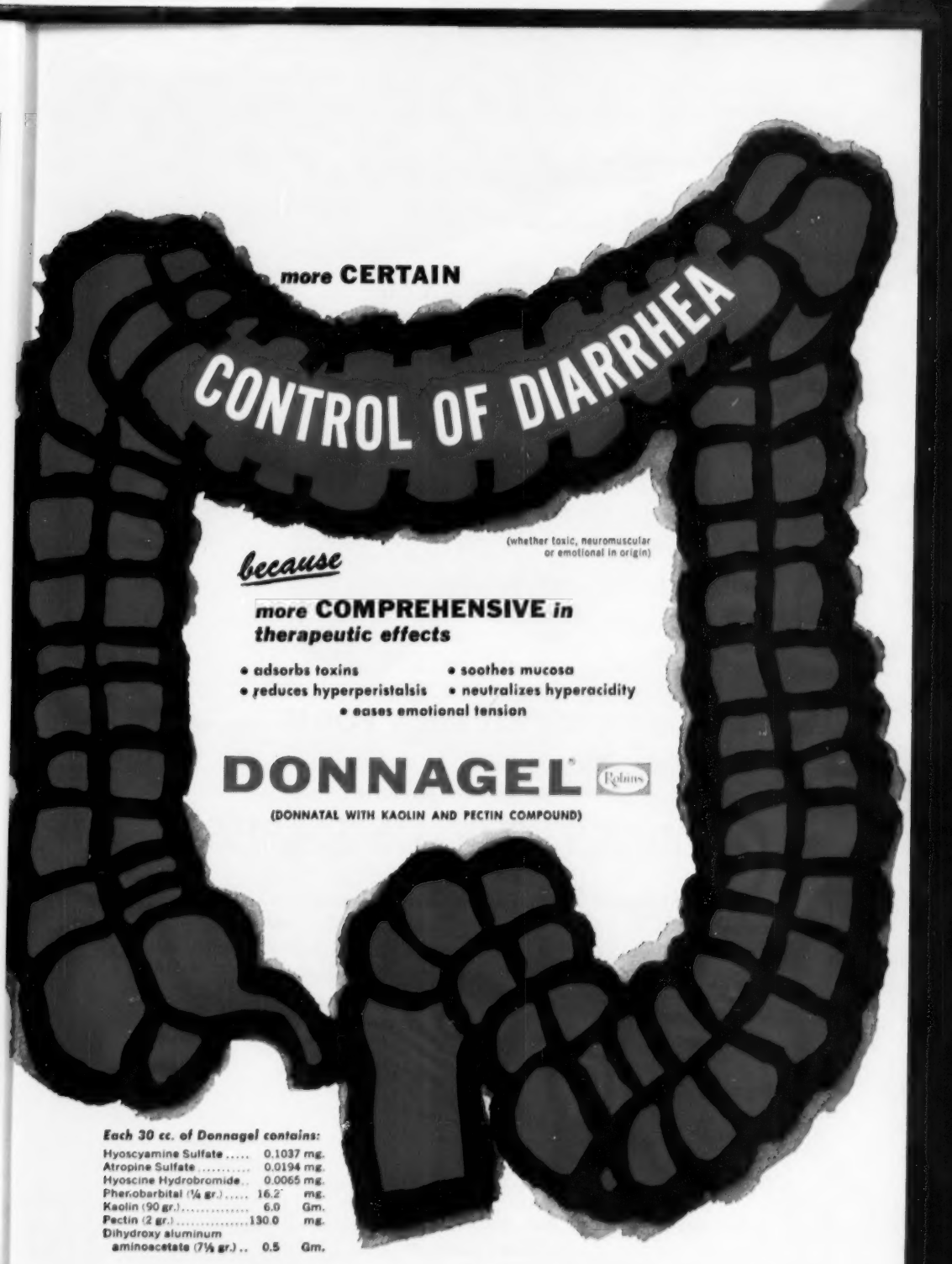

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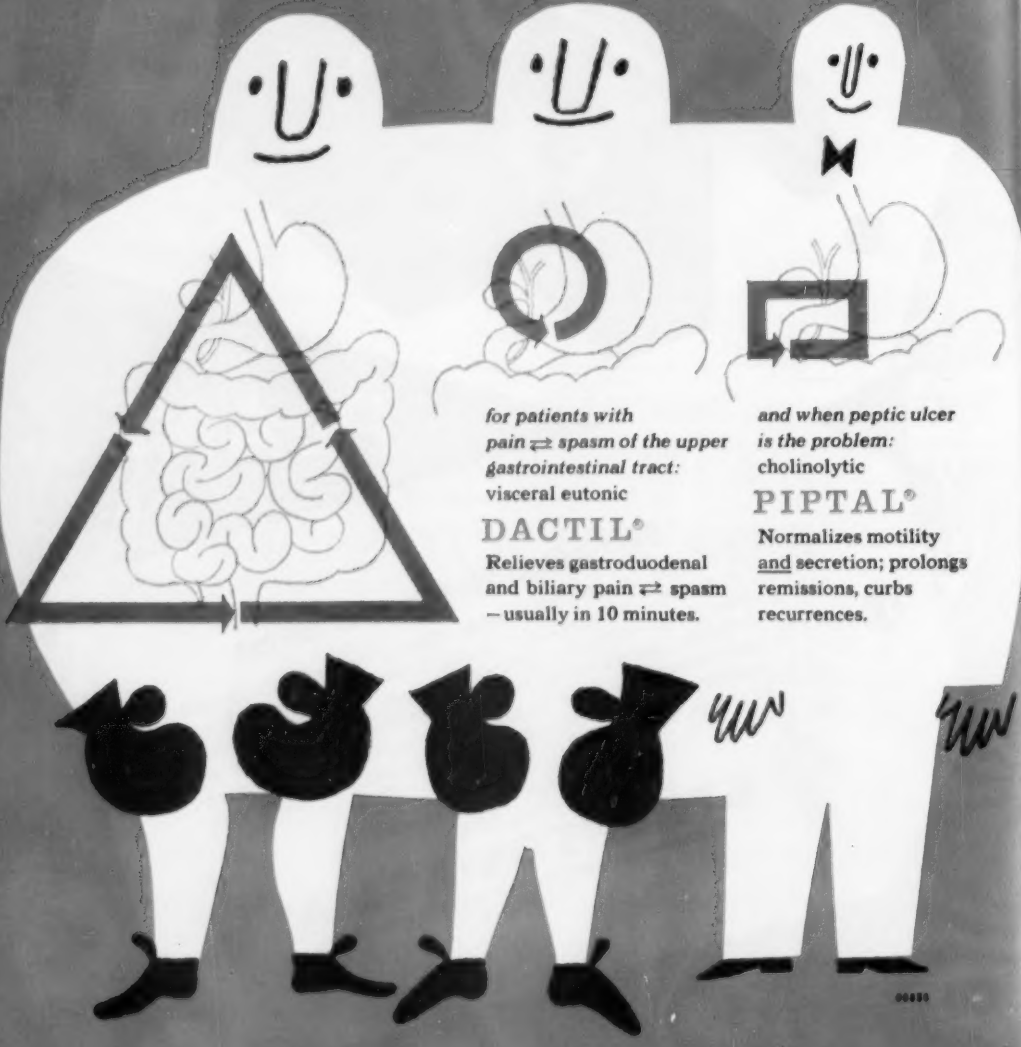

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DAA: Its Antacid Effect and Use in Peptic Ulcer

J. ALFRED RIDER, M.D., JOHN O. GIBBS, M.D., JOYCE SWADER, B.S., LEO VAN DER REIS, M.D., and JENNIE LEE, M.D.

ALUMINUM HYDROXIDE GEL is a widely used and effective antacid, but it has several disadvantages. The dried aluminum hydroxide gel, the most convenient form of this preparation for general use, varies in chemical properties, depending upon the source from which it is obtained,[1-3] and its acid-adsorbing and neutralizing capacities are slow in action. Therefore, there has been a continuing search for other antacid aluminum compounds.

A promising solid aluminum-containing preparation, dihydroxy aluminum aminoacetate (DAA), has been prepared by Krantz *et al.*,[4] who were impressed with "its prompt and prolonged buffering of acid." In terms of the aluminum content it is 42 per cent more efficient in acid-consuming power than dried aluminum hydroxide gel, and its buffer capacity is approximately six times greater. Murphey[5] found that, in contrast to the dried aluminum gel, DAA does not show a decrease in reactivity with time. Another advantage of this agent is that its buffering capacity is not appreciably diminished by gastric

From the Gastrointestinal Clinic, Department of Medicine, University of California School of Medicine, San Francisco, Calif.

The material in this report was presented in part as a scientific exhibit at the Atlantic City meeting of the American Medical Association, June, 1955.

The DAA used in this study was Robalate, a product of A. H. Robins Co., Richmond, Va.

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pepsin, whereas that of the dried aluminum hydroxide gel is greatly inhibited. Paul and Rhomberg[6] reported that they had found DAA effective in the treatment of 44 cases of peptic ulcer.

It is the purpose of the present paper to report the antacid effects of DAA on hydrochloric acid in vitro and in vivo, and the results obtained from its use in the clinical treatment of 65 cases of acute and chronic peptic ulcer.

CHEMICAL AND PHARMACOLOGIC PROPERTIES

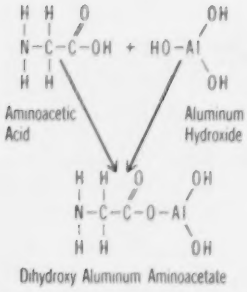


Fig. 1. **Formula of DAA and its relationship to aluminum hydroxide.**

The formula and the relationship of DAA to aluminum hydroxide is shown in Fig. 1. DAA has a molecular weight of 135.05; the aluminum atom makes up 19.97 per cent of the total weight. Aluminum hydroxide has a molecular weight of 77.99, of which 34.58 per cent is due to aluminum.

DAA is a stable, white, bland-tasting powder which goes rapidly into colloidal suspension in water. As an acid-buffering agent it has a prompt action and a prolonged effect. Rossett and Rice found by in vitro studies that DAA in tablet form was more reactive than straight aluminum hydroxide magma including an equivalent amount of its own liquid counterpart.[7] It is also a demulcent and mild astringent. The amino-acetic group present in DAA prevents the formation of molecular aggregates and acts as a dispersing agent to maintain chemical reactivity. In contrast, aluminum hydroxide is actually a hydrated aluminum oxide, with the water so loosely bound that it is removable by the ordinary process of drying at room temperature. The removal of water is an irreversible procedure; once dry, aluminum oxide has very little reactivity. This probably accounts for the instability of many of the tablet preparations of dried aluminum hydroxide.[8]

METHODS AND MATERIALS

In Vitro Antacid Effects of DAA and Aluminum Hydroxide

Several test solutions, made by adding 50 cc. of 0.1N hydrochloric acid to 95 cc. of water, were put into beakers and kept at 37°C. in a water bath. Crushed tablets of aluminum hydroxide and of DAA in

amounts ranging from 0.5 to 2 Gm. were added to separate beakers. The contents were stirred continuously while pH determinations were made, using a Beckman Model G pH meter, at 5-minute intervals for 15 minutes and then every 15 minutes for the remainder of a 2-hour period.

In Vivo Antacid Effect of DAA

Subjects were selected for study on the basis of 1-hour basal gastric analyses performed immediately preceding the test. Only those were used as subjects who had free acid in each of the four 15-minute basal specimens and at least 20 clinical units of free hydrochloric acid in one or more of the samples.[9]

When these criteria were met, DAA, in amounts of 0.5, 1, or 2 Gm. dissolved in 5 cc. of water, was instilled into the subject's stomach via a Rehfuss tube. The tube was immediately rinsed with an additional 5 cc. of water. Following this, approximately 5 cc. of the gastric contents were withdrawn every 15 minutes during a 2-hour period. The pH of these samples was determined and compared with the pH of the 4 basal specimens which had been collected during the first hour.

A similar but larger group of patients was studied by the same technic to determine the duration of anacidity. For this purpose the test was terminated as soon as free acidity returned (pH less than 3.5).

Clinical Effects of DAA in Peptic Ulcer

Sixty-five unselected patients with peptic ulcer were used for clinical testing. The majority of these patients were seen in the Peptic Ulcer Clinic because they had not done well on a variety of medical programs which, by and large, were reasonable but frequently not very strict. Most of these patients were considered to have "chronic" or "resistant" ulcers, since they had persistent symptoms, but at times it was difficult to determine whether the patient, the doctor, the ulcer, or any combination of these factors was responsible.

Initially, the patients were given a Sippy III or Sippy IV diet; later a "bland diet" was substituted in the majority of cases. DAA was given orally in amounts of from 0.5 to 1 Gm. 3 or 4 times daily to patients with less frequent symptoms and in doses as high as 1.5–2 Gm. each hour to those who reported almost constant symptoms. In general, the smallest dose required to keep the patients asymptomatic, or almost so, was used.

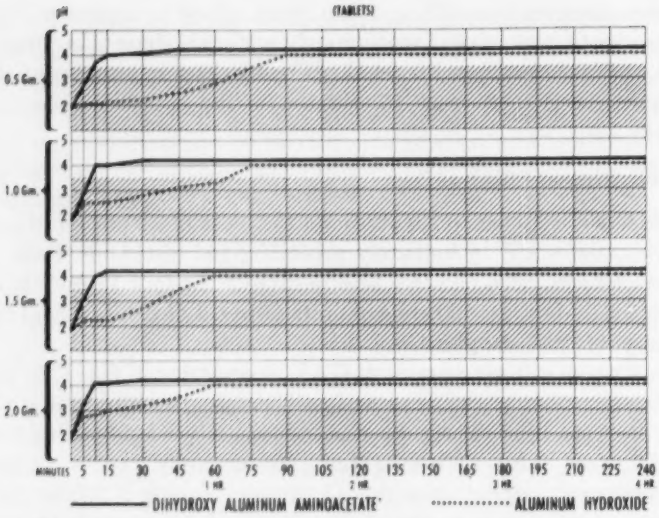


Fig. 2. In vitro comparison of DAA with aluminum hydroxide

RESULTS

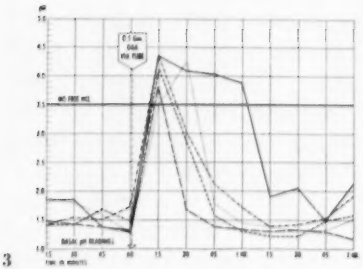
Comparative in Vitro Effects of DAA and Aluminum Hydroxide

As shown in Fig. 2, DAA reached equilibrium more rapidly than aluminum hydroxide and effected a slightly higher rise in pH. Within 10 minutes the pH was raised from 1.9 to more than 3.5. Within 30 minutes the highest pH, 4.28, was reached except for the solution containing 0.5 Gm. of DAA, which required 45 minutes. Thus, the quantity of DAA used had no striking effect upon the rapidity of rise of the pH. In contrast, aluminum hydroxide required 60 minutes to achieve a peak rise to a pH of 4.12. Thus, both compounds raise the pH above the accepted therapeutic range of 3.5.

In Vivo Effects of DAA

Fifteen patients were tested with 0.5, 1, and 2 Gm. of DAA (Figs. 3, 4, and 5). In general, it was observed that the greater the dose, the longer the duration of anacidity. In only 1 case did the effect persist for more than 1 hour. In all patients given the 2-Gm. dose, anacidity persisted for 45 or more minutes, but with the 0.5-Gm. dose the duration of anacidity exceeded 15 minutes in only 2 cases.

In 48 additional patients an attempt was made to correlate the maximum basal gastric free acidity with the duration of anacidity pro-



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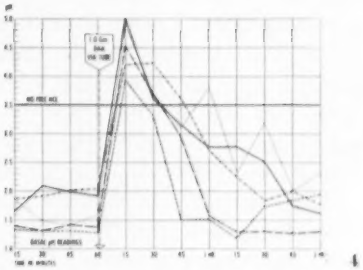

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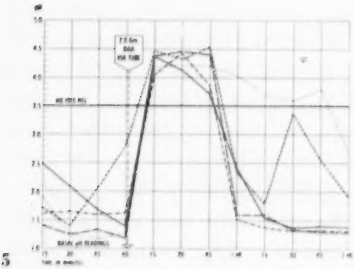

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Fig. 3. **Individual pH curves of gastric juice following single oral doses of 0.5 Gm. DAA (in 5 patients).** *Fig. 4.* **Same as Fig. 3, but with 1.0 Gm. DAA.** *Fig. 5.* **same as Figs. 3 and 4, but with 2.0 Gm. DAA.**

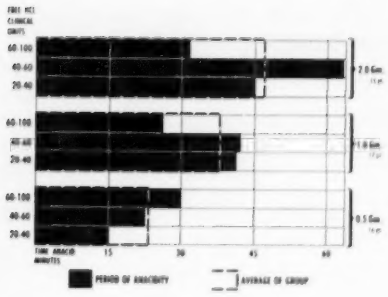

Fig. 6. **Duration of anacidity correlated with size of therapeutic dose and degree of gastric acidity.**

duced by DAA in amounts of 0.5, 1, and 2 Gm. (Fig. 6). Again, the greater the dose, the longer the average duration of anacidity. The antacid effect of the 1- and 2-Gm. doses on the patients with the highest basal acid levels was not as great as that obtained in those with acid levels in the lower range.

Clinical Results in the Treatment of Peptic Ulcer

The 65 patients treated ranged in age from 23 to 76 years; there were 19 females and 46 males. Fifty of these patients had a duodenal ulcer,

10 a gastric ulcer, 4 a jejunal ulcer, and 1 patient both a duodenal and a gastric ulcer. The maximal basal free gastric acidity ranged from 3 to 98 clinical units in those with a duodenal ulcer and from 0 to 68 clinical units in those with a gastric ulcer. The one patient without basal free acid did have free acid on histamine stimulation. The free acidity in the patients with jejunal ulcers ranged from 28 to 55 units. The duration of treatment varied from 4 to 38 weeks.

Thirteen patients received 0.5–1 Gm. of DAA 3 or 4 times a day; 41 patients received 0.5–1 Gm. every 2 hours; 9 patients received 0.5–1 Gm. every hour; and 2 patients received 1.5–2 Gm. every hour. On this program and with either a Sippy III or IV diet, which in most cases was later changed to a "bland diet," 40 patients (61.5 per cent) were asymptomatic and 17 patients (26.2 per cent) had only rare symptoms. Thus, 57 patients (87.7 per cent) were classified as showing a good or excellent response. Six patients (9.2 per cent) continued to have symptoms, but these were less frequent and not as severe; they were classified as showing only a fair result. Two patients (3.17 per cent) showed no improvement. One of these could not tolerate the drug because the taste caused nausea. This appeared to be due to the added flavoring agent, since an unflavored tablet did not cause this symptom. Five patients complained of constipation. Thus, a total of 9.2 per cent of patients had side effects, but in only 1 case were these of sufficient severity to warrant discontinuing the therapy.

SUMMARY and CONCLUSIONS

1. Dihydroxy aluminum aminoacetate (DAA) is an effective, stable antacid with a prompt action and prolonged effect. In tablet form it is pleasant and simple to take.

2. In vitro studies show that DAA reaches equilibrium more rapidly and achieves a slightly higher pH than comparable amounts of aluminum hydroxide. The quantity of DAA used has little effect on the time required.

3. In vivo studies reveal that the length of the antacid effect depends upon the dose and the basal gastric acidity.

With the 2-Gm. dose anacidity persisted on the average for more than 45 minutes.

With the 0.5-Gm. dose the average was between 15 and 30 minutes.

Usually, but not always, the antacid effect of DAA in the patients with the highest basal acid levels was not as great as that obtained in those with acid levels in the lowest range.

4. Sixty-five patients, the majority of whom had a "chronic" or persistent peptic ulcer, were treated with DAA and diet.

A good or excellent result was obtained in 87.7 per cent of these patients.

Mild side effects, usually constipation, were manifested by 9.2 per cent.

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Positional Relation of Gallbladder to Hepatic Flexure

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THE anatomic relationships of the gallbladder are described in the standard textbooks of anatomy, surgery, and diagnostic roentgenology. The related organs which are generally mentioned include the liver, colon, and duodenum. An association to the transverse colon and second portion of the duodenum is often suggested but not clearly spelled out. A constant affinity to the liver is generally emphasized.

One of us (H.G.J.) has had the impression for some time that a constant relationship exists between the gallbladder and hepatic flexure.* We have not been able to find this point stressed or even mentioned in any of the radiologic literature. Only one anatomic treatise[1] mentions that the fundus of the gallbladder is near the hepatic flexure. The present study was undertaken to determine the frequency of such a relationship and to evaluate its importance if found to be present.

MATERIAL AND METHOD

This report is based on a review of 419 consecutive oral cholecystograms in which an opacified gallbladder could be visualized. The material collected covers a 2-year period in an adult group with a 2:1 ratio of female to male patients. The following films were usually available with each oral cholecystogram: posteroanterior erect, posteroanterior prone, left anterior oblique prone, post (1 hour) fatty meal, usually posteroanterior or left anterior oblique prone.

The results were tabulated, indicating the distance between the hepatic flexure and the gallbladder. Mention was made of any change

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* First pointed out in 1942 at Yale University School of Medicine by Dr. Hugh M. Wilson, presently Professor of Radiology, Washington University School of Medicine.

in the relationship of these two structures in the standard positions or after the fatty meal. On actual measurements the distance between the upper portion of the hepatic flexure and the lowermost portion of the gallbladder fundus was the recorded figure.

Of the 419 cholecystograms available for study, 3 were excluded because of the following findings:

1. Situs inversus in which the gallbladder-hepatic flexure relationship could not be determined.
2. Hepatoma.
3. Interposition of the hepatic flexure between the liver and the right diaphragmatic leaflet.

In the latter two instances the gallbladder was 15 and 6 cm., respectively, from the hepatic flexure. These special circumstances would seem to justify the exclusion of these cases. Of the remaining 416 cases, there was insufficient gas or fecal material in the hepatic flexure to determine an association in 11 cases, or 2.6 per cent. It was thus possible to determine the gallbladder-hepatic flexure relationship in 405 of 416 cases (97.4 per cent) (Table 1). The gallbladder was considered to be *closely* related to the hepatic flexure if the distance separating the two organs was less than 3 cm. This was found to be true in 384 of the 405 cases considered suitable for study, or an incidence of 94.8 per cent.

RESULTS

In the group of 384 cases in which this close proximity existed, 257 were contiguous, (the gallbladder was in direct contact with the hepatic flexure) 65 were from 1 cm. to less than 2 cm., and 62 were from 2 cm. to less than 3 cm. from the hepatic flexure. Fig. 1 is illustrative of cases showing contiguous contact. Thus there were 21 cases considered "distantly removed," or 5.2 per cent. In these 21 cases the same approximate 2:1 preponderance of females prevailed as in our entire

TABLE 1. Gallbladder-Hepatic Flexure Relationships

Position of gallbladder	No.		%
Closely related		405	97.4 (of available cases)
Contiguous with hepatic flexure	257		63.5
From 1 to less than 2 cm. distant	65		16
From 2 to less than 3 cm. distant	62		15.3
Distantly removed from hepatic flexure		21	5.2

Hepatic flexure not seen in 11 cases.

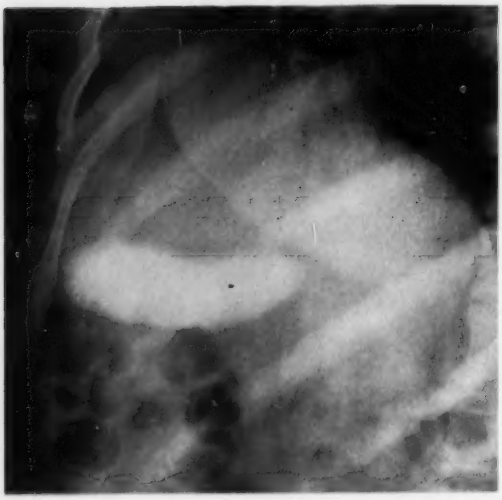

Fig. 1. **The gallbladder is seen to be contiguous with the hepatic flexure.**

series. These statistics confirm our impression of the close approximation of the gallbladder to the hepatic flexure.

In the erect position, the gallbladder was at times noted to move toward the midline. Although in these cases the gallbladder becomes more removed from the hepatic flexure with this shift in position, it still maintains a close proximity to the transverse colon.

These measurements usually held similarly for both frontal-plane and left-anterior-oblique projections. In some instances the relationship was close in one plane and not the other. In such a situation we accepted the projection in which the gallbladder-hepatic flexure relationship was close.

Colonic Visualization

Twenty-four cases were studied in which the colon was opacified with barium or filled with air after oral cholecystography in order to further establish the close connection already demonstrated. In all of these instances, the same relationship was noted. Figure 2 demonstrates such a case after colon opacification and Figure 3 is an example of air insufflation of the colon with cholecystography. Surprisingly, there generally appears to be very little, if any, change in the pre- and post-evacuation barium-filled films of the colon as relates to the gallbladder-hepatic flexure distance.

Fig. 2. **The proximity of the gallbladder to the hepatic flexure is demonstrated by opacification of the colon with barium.**

DISCUSSION

The high frequency of juxtaposition of the gallbladder to the hepatic flexure can be explained on the basis of certain embryologic, anatomic, and radiologic data.

The gallbladder develops from the gut entoderm in the region of the floor of the future duodenum. Within its fossa in the liver the gallbladder is attached to the liver by fibrous connective tissue and possesses a posterior peritoneal covering. Additional fixation is probably afforded by the gastrohepatic, hepatoduodenal, and gastrocolic ligaments. Although the hepatic flexure shows mobility with change from the supine to the erect positions, the shift in position is accompanied by coincident movement of the liver and gallbladder, so that relationships are generally maintained (although we have noted that the gallbladder was found frequently to [18.9 per cent] move medially with assumption of the upright posture).

Gallbladder-Liver Relationship

From the radiologic point of view, the gallbladder-liver relationship

Fig. 3. **Following air insufflation of the colon the gallbladder is noted to be contiguous with the hepatic flexure.**

Fig. 4. **A group of concretions is present in the right upper abdomen partially overlying the eleventh rib. Note that the concretions are distantly removed from the barium - opacified hepatic flexure.**

is impractical for use, since it is difficult to delineate the visceral border of the liver. Thus no point of contiguity can be established. The gallbladder-duodenal proximation cannot usually be ascertained in

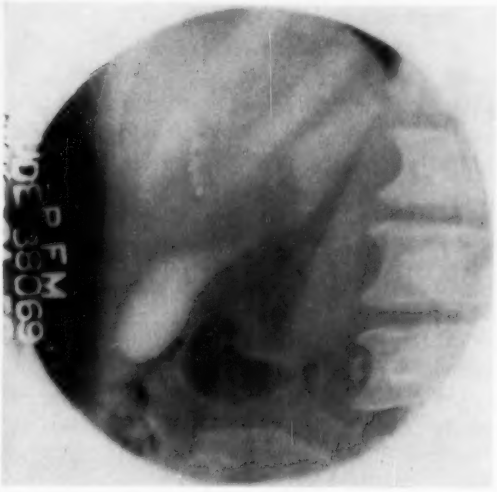

Fig. 5. **The same case as shown in Fig. 4. This confirms the impression that the concretions in the right upper quadrant are not in the gallbladder.**

radiologic practice unless oral barium is administered. Further, we have found such a relationship to be quite variable.

Gallbladder-Colon Relationship

The gallbladder-colon relationship remains to be considered. In view of the above-mentioned anatomic and radiologic facts, the gallbladder seems to be sufficiently checked in position, so that its most frequent point of close contact is the hepatic flexure. The frequent finding of gas and/or fecal material in the hepatic flexure thus permits the delineation of both the hepatic flexure and gallbladder during cholecystography.

Significance of Close Gallbladder-Hepatic Flexure Relationship

The proximity of the gallbladder to the hepatic flexure of the colon has practical significance in a roentgen study of the gallbladder region. A diagnosis of cholelithiasis can be made with reasonable certainty on a scout film of the abdomen if calcareous structures present are close to the hepatic flexure. We have recently seen several cases in which this applicability was well demonstrated. In an occasional case, air

can be instilled per rectum to outline the hepatic flexure if it is not otherwise seen. Those calcifications distantly removed from the hepatic flexure (3 cm. or more) are most likely not in the gallbladder. In Fig. 4 concretions are seen in the right upper quadrant quite distantly removed from the hepatic flexure. Our impression that these concretions did not represent gallstones is confirmed in Fig. 5. Additionally, the search for a faintly opacified gallbladder in cholecystography can safely be concentrated around the hepatic flexure area.

Absence of Relationship

In that small percentage of cases in which no close contact exists between the gallbladder and hepatic flexure, the explanation may lie in the presence of a mesentery for the gallbladder or the hepatic flexure which is occasionally present.[1] A scarred and contracted gallbladder resulting from inflammatory disease could also account for lack of a close relationship.

CONCLUSIONS

1. A close anatomic relationship exists roentgenologically between the gallbladder and hepatic flexure of the colon, as shown in a series of 419 cases.

2. This approximation is of practical importance in the evaluation of calcareous deposits in the right upper quadrant of the abdomen.

3. The proximity between the gallbladder and hepatic flexure may be of assistance in locating a faintly opacified gallbladder during cholecystography.

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Prolonged Anticholinergic Therapy of Duodenal Ulcer

DAVID CAYER, M.D.

THE MAGNITUDE of the ulcer problem is indicated in some measure by the estimate that 10 per cent of the population of this country will at some time have an active peptic ulcer.[1] Duodenal ulcer may develop at any age. It is being recognized with increasing frequency in children and undoubtedly occurs more often than is ordinarily suspected.[2]

In acute, uncomplicated duodenal ulcer the prognosis for life is excellent, though the frequency of recurrence is high. Exacerbations are so characteristic that they often help to establish the diagnosis. A review of numerous articles on the subject indicates considerable variation in the reported incidence of recurrence—the figures ranging from 9 to 80 per cent for recurrences within 1 year and from 46 to 87 per cent for recurrences within 2 years.[3-6] The general consensus, however, is that 44 per cent of patients treated for active duodenal ulcer will have a recurrence within 1 year and 74 per cent within 2 years. Few figures are available on long-term follow-up studies, but it seems agreed that 30 per cent or less of patients with duodenal ulcer will be asymptomatic for as long as 5 years. In view of this high relapse rate, an evaluation of the long-term effects of treatment seems indicated.

Difficulties Inherent in the Management of Ulcer

The purpose of treatment is to control symptoms, to promote healing, and to prevent recurrences. The last aim continues to present the greatest problem. Medical treatment, even by diet alone, usually affords prompt and complete relief of symptoms in patients with uncomplicated duodenal ulcers. The outlook for permanent cure under medical management, however, is unfavorable. Ulcer patients tend to have periodic recurrences. The effects of ulcer therapy, therefore, are

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difficult to evaluate except by careful and prolonged follow-up. There are few reported observations made on patients under *prolonged continuous treatment*. The asymptomatic patient discontinues treatment and rarely returns to the physician unless his pain recurs. Patients often resent and are unable to follow long-term, inflexible therapeutic regimens calling for frequent doses of expensive medication, and willingly accept treatment only for relief of pain.

Etiology of Duodenal Ulcer

The general theories of etiology have been fully expounded in the literature, and will not be discussed here except as they relate to the vagus nerve and to the effects of anticholinergic drugs on the activity of this nerve. The weight of evidence favors the secretion of acid pepsin as the prime factor in maintaining ulcer activity and in producing ulcer recurrence. Prolonged hypersecretion with associated hyperemia appears to be the forerunner of mucosal ulceration. The contact with acid gastric juice perpetuates the lesion.

Among the factors whose interplay can produce hyperacidity and increased peptic activity with associated hyperemia are emotional or psychogenic changes and hormonal stimulation, as well as the effects on the endocrine glands of circulatory changes, infection, and fatigue. The effects of chronic anxiety and tension states in producing hypermotility and hyperacidity, with altered gastric circulation, have been stressed, as have disturbances of the posterior hypothalamus mediated by way of the vagus and splanchnic nervous systems. While many of the factors responsible for hypermotility and hypersecretion are known, those accounting for lowered resistance of the affected areas continue to elude the investigators. The fact that total gastric volumes and the degree of acidity may be higher when the patient is asymptomatic than when his ulcer is active is well recognized.

Effects of Anticholinergic Drugs

It has been felt for a long time that the medical management of peptic ulcer would be facilitated greatly by a satisfactory antisecretory drug. Varying degrees of effectiveness have been attributed to the newer anticholinergic preparations. Anticholinergic drugs, particularly when given parenterally, result in prompt relief of pain due to peptic ulcer. Oral administration also produces this effect, although to a less pronounced degree. A reduction in free hydrochloric acid is a frequent but inconstant finding. The most marked effect is on motility, particularly when duodenal spasm, excessive peristalsis, and disturbances

in gastric evacuation are present.[7] Under such circumstances relief of pain can be shown to coincide with cessation of motility, in spite of the persistent demonstrable presence of high gastric acidity and active ulceration. The possibility of a central analgesic action has not been eliminated, nor has that of local anoxemia due to vascular spasm.

The fact remains that the ultimate test of the efficacy of any antiulcer regimen is its effect on the recurrence rate and the incidence of complications in patients having duodenal ulcers. Initial reports have intimated that certain anticholinergic drugs are so effective in the treatment of peptic ulcer that there is no longer a need for diet or antacids, that patients can continue to smoke, and that surgery for peptic ulcer is a thing of the past. Results of subsequent studies have provided less optimistic conclusions.[8]

Principles in Evaluation of a New Therapeutic Agent

In order to determine accurately the value of any new drug, it is necessary to eliminate or minimize the possibility of coincidental spontaneous remissions, the effects of psychotherapy, and errors in judgment on the part of the investigator. Certain fundamental principles which must be observed in such an investigation are as follows:

1. The groups of patients should be similar in age and in social and economic circumstances.

2. A sufficiently large number of patients should be included. The more patients studied, the more significant are differences between various forms of treatment.

3. The groups should be given identical treatment, with one exception: drugs *versus* placebos. The medication being tested must be compared with a placebo similar in appearance, frequency of dosage, and flavoring.

4. The study must be a "double blind" one. It is essential that neither the patient nor the investigator know the nature of the medications being used. The beneficial effects of frequent, careful follow-ups, as well as the interest of the doctor, are well recognized and are important factors in treatment. The investigator, if aware which drug is a potentially potent therapeutic agent, may unconsciously by word or action transmit his feeling of enthusiasm to the patient, with the result that an unprejudiced evaluation of the drug is not possible.

5. A daily record, including all criteria necessary for recognition of the clinical state of the disease, should be kept by the patient. Some studies designed to evaluate a new drug have been based on the patient's recollection or inadequate records on the frequency and severity

of his symptoms. A daily analysis of his symptoms should be recorded by the patient on a form card, which can be presented to the physician at regular intervals for review. In this manner, fluctuations in the course of the disease can be checked against the results of the examination as well as against the patient's estimation of progress.

6. An adequate period of follow-up should be allowed. In a disease with a recurrence rate over a period of 24 months as high as 60 to 70 per cent, it goes without saying that it is unwise to attribute apparent improvement during a short interval to the effects of any form of therapy. The observation period should extend beyond the interval during which one might ordinarily anticipate a recurrence. Numerous reports have praised the efficacy of drugs employed for a treatment period of 1 month!

7. The data should be subjected to statistical analysis in order to remove the necessity for "clinical impressions" on the part of the investigator.

STUDY ON PROLONGED ANTICHOLINERGIC THERAPY

This study was undertaken in the hope that it would provide the answers to the following questions:

1. Does the patient with active duodenal ulcer who is taking anticholinergic drugs daily in recommended doses fare better over a long period than one who is not taking such drugs?
2. Will such patients have fewer or less severe recurrences?
3. Are complications less frequent with such therapy?
4. Will the number of patients requiring surgery be decreased by the use of these drugs?

MATERIALS AND METHODS

One hundred and sixteen patients were studied for periods varying from 7 to 13 months and averaging 10.5 months. This group included 111 males and 5 females, ranging in age from 22 to 58 years with a mean age of 37.1. The average duration of symptoms was 8.2 years; the shortest was 1 year, the longest 30 years. Patients with pyloric obstruction were excluded. The average number of recurrences per year, on the basis of history, was 2.8. Eight patients had not had a recurrence in the preceding 2 years. Twenty-three patients had a past history of hemorrhage; 7 had had multiple hemorrhages. Nine patients had had perforations which were treated surgically by closure of the perforation. Each patient had a history indicating peptic ulcer activity within six months preceding the study, and 16 patients stated that they

were having fairly constant discomfort. At the onset of the study, all patients had clinical signs and symptoms of activity, and a duodenal ulcer was diagnosed by roentgen examination in every instance.

The duration, frequency, and severity of ulcer symptoms were determined at the onset of treatment and classified as mild, moderate, or severe. The symptoms were considered as mild in 14 patients, moderately severe in 78, and severe in 24. Antacids and a bland diet with 6 feedings per day were prescribed for all patients.

Medication

Medications used in the experimental study consisted of tablets identical in appearance, each containing either 50 mg. of Banthine,* 15 mg. of Pro-Banthine,* 25 mg. of Pathilon,** 0.2 mg. of atropine, or a placebo. The average daily doses were as follows: Banthine, 400 mg.; Pro-Banthine, 120 mg.; Pathilon, 200 mg.; and atropine, 1.6 mg. All patients were seen at intervals of 1–3 months, and roentgen examinations were made at appropriate times (an average of twice a year). All medications were given to the patients without cost. Neither patient nor physician knew which medication was being used.

Evaluation of Clinical Status

Final evaluation of the results in each case was based on data recorded by the patient and the clinical impression of the investigator at each follow-up visit. The difficulties involved in evaluating the degree of duodenal deformity by roentgen examination are obvious, and this method was not employed as one of the diagnostic criteria. The patient's clinical status was classified in three ways, as follows:

Results

Good to Excellent. Freedom from ulcer distress throughout the period of observation or improvement in spite of periodic recurrences.

Fair to Poor. Exacerbation, no change, or only slight improvement, with continued recurrences.

Recurrences

None
Fewer and milder
Same
More

* Furnished through the courtesy of the G. D. Searle Company, Chicago, Ill.

** Furnished through the courtesy of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Complications under Treatment

Hemorrhage
Obstruction
Perforation
Surgery needed for relief.

RESULTS

Five patients ultimately discontinued the anticholinergic drugs because of the side effects. Four other patients discontinued them because they felt that the drug aggravated their symptoms.

The results of therapy in the patients studied may be summarized as follows (Table 1): With the anticholinergic drugs employed (Banthine, Pro-Banthine, and Pathilon) and in the dosage used, *good to excellent results* were obtained in an average of 70 per cent of the patients studied, varying from 56 per cent in the patients on Pro-Banthine to 76 per cent in those receiving Pathilon and Banthine. *Fair to poor results* were found in an average of 30 per cent of the patients on anticholinergic drugs. The results in patients receiving placebos or atropine were almost equally divided between the "good to excellent" and the "fair to poor" categories.

Statistical analysis of these figures reveals that the patients receiving Banthine and Pathilon fared significantly better than those receiving atropine or placebos.

TABLE 1. Effects of Drugs on the Course of Peptic Ulcer

	Placebo	Atropine	Banthine	Pro-Banthine	Pathilon
Daily dose	8 tabs.	1.6 mg.	400 mg.	120 mg.	200 mg.
No. patients and length of follow-up	15, 7 mo.	37, 11 mo.	27, 13 mo.	16, 9 mo.	21, 11 mo.
Results					
Good to excellent	7 (47%)	19 (51%)	20 (74%)	9 (56%)	16 (76%)
Fair to poor	8 (53%)	18 (49%)	7 (26%)	7 (44%)	5 (24%)
Recurrences					
None	4 (27%)	6 (16%)	6 (22%)	2 (13%)	4 (19%)
Few	4 (27%)	17 (46%)	13 (48%)	8 (50%)	12 (57%)
Same	7 (46%)	14 (38%)	8 (38%)	6 (38%)	5 (24%)
Complications					
Hemorrhage	0	2 (5%)	2 (7%)	3 (19%)	2 (9.5%)
Performation	0	0	1 (4%)	0	0
Obstruction	0	0	1 (4%)	0	0
Surgery needed	0	1 (3%)	1 (4%)	1 (6%)	0
Side effects					
Oral	1 (7%)	14 (38%)	21 (78%)	4 (25%)	3 (14%)
Visual	0	4 (11%)	13 (48%)	1 (6%)	0
Sphincter	0	4 (11%)	4 (15%)	0	0

Recurrences

Twenty-nine per cent had as many as or more than they had had previously, while the remainder (52.3 per cent) were considered to have had fewer or milder recurrences. Only 18.7 per cent of the patients taking anticholinergic drugs were asymptomatic during the entire period of study. Comparison with control groups showed no statistically significant difference.

Complications

It is obvious that, in spite of all the precautions of a carefully planned experiment, the evaluation of subjective manifestations may continue to present some problems. There is nothing equivocal, however, about the occurrence of melena, hematemesis, perforation, or obstruction.

Hemorrhage occurred in 10.9 per cent of the patients receiving the anticholinergic drugs and in only 5 per cent of the patients receiving atropine or placebos. The small number of patients, however, and the difference in the periods of follow-up for the groups rendered the results statistically insignificant. Only 1 case of pyloric obstruction developed, and this was in the group of patients receiving anticholinergic drugs. The percentage of patients ultimately requiring surgery was essentially the same among those receiving anticholinergic drugs as among those receiving atropine.

A significantly higher incidence of recurrences as well as complications was observed in patients who gave a past history of hemorrhage or perforation.

DISCUSSION

Peptic ulcer is a disease which is subject to spontaneous remissions and frequent exacerbations. Evaluation of any therapeutic agent used in the treatment of such a disorder requires a carefully controlled study. The fact that patients become asymptomatic while under treatment does not necessarily prove the medication to be effective.

Unfortunately, the evaluation of many so-called antispasmodic drugs has often been based on impressions rather than facts. Such drugs have been added to the usual therapeutic regimen of diet, sedation, antacids, psychotherapy, and general supportive measures, and the results appraised without any attempt to control the numerous variables. In the present study, each patient's past history served as his control. In addition, a standard plan of treatment was utilized, and control groups taking atropine or a placebo were included in the study. All the patients studied had an active ulcer at the onset of treatment,

and a history indicating a chronic condition with frequent recurrences. Over a period of time during which one might ordinarily anticipate a recurrence they were maintained continuously on drugs in dosages considered to be therapeutically effective.

Precipitating Factors in Recurrence

In those patients whose ulcers became reactivated while under treatment, an effort was made to determine the existence of any possible precipitating cause. The most common factors which appeared to be of any significance were, in order of frequency, mental and physical strain, fatigue,[12] and intercurrent infection, usually upper respiratory, combined with the ingestion of medications containing aspirin or salicylates.[3] In the majority of cases, however, no obvious cause for recurrence could be found.

Diet

The components of the diet which the patient followed did not seem to be a significant factor. Those patients who adhered to more rigid diets had no fewer recurrences than those who interrupted or discontinued their diets. The development of poor and irregular eating habits, with long intervals between meals and particularly before bedtime, seemed to be more important. Since the majority of patients who went off their diets did so long before symptoms recurred, there appears to be no strong or immediate relationship between dietary indiscretions and the reactivation of ulcer.

Use of Tobacco

The majority of the patients were tobacco users and continued to smoke throughout the period of observation and treatment. While the relation of tobacco to the production of peptic ulcer and its effect on management of the active lesion are not clear, smoking does have a demonstrable effect on gastric acidity. It is important, however, to recognize that excessive smoking often mirrors an increase in nervous tension. The same may be said of alcohol, which also has a direct chemical effect on the mucosa. It is the opinion of most observers that healing of peptic ulcer is facilitated when smoking is limited or discontinued. Frequently the cessation of smoking is associated with a considerable increase in appetite, which itself is of value if it permits the patient to follow a regular schedule of more frequent feedings.

Effectiveness of Anticholinergic Drugs

That anticholinergic drugs relieve pain and possibly facilitate healing of a peptic ulcer is generally accepted. The data being reported

would suggest that the results obtained in patients maintained on adequate dosages of anticholinergic drugs are better than those noted in patients receiving similar supportive treatment plus atropine in the dosage noted. It is equally apparent that present methods of treatment, while they assist in the production of a remission, do not prevent recurrences. The incidence of complications such as hemorrhage, perforation, or other conditions requiring surgery is essentially unchanged.

SUMMARY and CONCLUSIONS

The treatment of acute or uncomplicated ulcer with anticholinergic drugs is effective and gratifying. Anticholinergic drugs, chiefly through their effect on gastrointestinal motility, are helpful in relieving ulcer pain and possibly in facilitating healing. In the present study of 116 patients, those receiving potent anticholinergic drugs in the dosage prescribed fared significantly better than those receiving atropine or placebos. However, recurrences, hemorrhage, perforation, and obstruction were not prevented by the constant administration of these drugs in the dosage used.

In all probability, rigid diets followed over prolonged periods have no major effect. More important are the patient's dietary habits and his schedule of eating.

Anticholinergic drugs should be used as adjuncts to conventional therapy, and never as substitutes for the time-proved measures. Treatment must continue to be based on a rational approach which has a reasonable likelihood of producing a favorable effect in each instance. Duodenal ulcer continues to be a therapeutic problem, and the development of new drugs has not obviated the need for rest, reassurance, sedation, antacids, diet, and other measures.

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Amebiasis: A Review

II. Laboratory Diagnosis, Differential Diagnosis and Therapy

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THE TROPHOZOITES OF *Endameba histolytica* are 18–25 μ in diameter, have clear hyalin ectoplasm and finely granular endoplasm which is less refractile and contains erythrocytes (Fig. 1). The pseudopodia are formed from the ectoplasm into which the endoplasm flows, thus moving toward the pseudopod. The nucleus is not visible in the living ameba, but in iron-hematoxylin preparations and iodine smears it has a centrally located pinpoint karyosome (chromatin) with a linin network of fine fibrils stretching from the karyosome to the finely granular and uniform peripheral chromatin on the nuclear membrane, like the spokes of the wheel. This nuclear morphology is constant in all stages of the ameba. The precysts are formed by the rounding up and shrinking of the trophozoites and the elimination of food vacuoles. There may be blunt pseudopodia. The precysts are nonmotile. The cytoplasm may contain rodlike hyalin bodies. The cysts are hyalin and round, have a thick cyst wall, and measure 3.5 to 20 μ in diameter, but average 12 μ. In the living cyst the nucleus is not visible. The cytoplasm may contain a vacuole and rodshaped chromatoidal bodies, and the mature adult cyst contains 4 nuclei. The metacysts are a group of 4 daughter invasive trophozoites which emerge through the cyst wall in the iliocecal region.

Endameba histolytica should not be confused with such caprozoic amebas as *Endameba coli*, *Endolimax nana*, *Iodameba buetschlii* and *Giardia lamblia* cysts which are flagellates. Recent reports indicate that *Dientameba fragilis* may invade the tissues and cause pathology. Although caprozoic amebas are nonpathogenic, their presence in the stools indicates fecal contamination of the intestinal tract of the host.

LABORATORY DIAGNOSIS

Stool Examinations

Since the output of the cysts occurs in cyclical crops, 3–10 stools (an average of 6) should be examined.

From the Columbia-Presbyterian Medical Center, New York, N. Y.

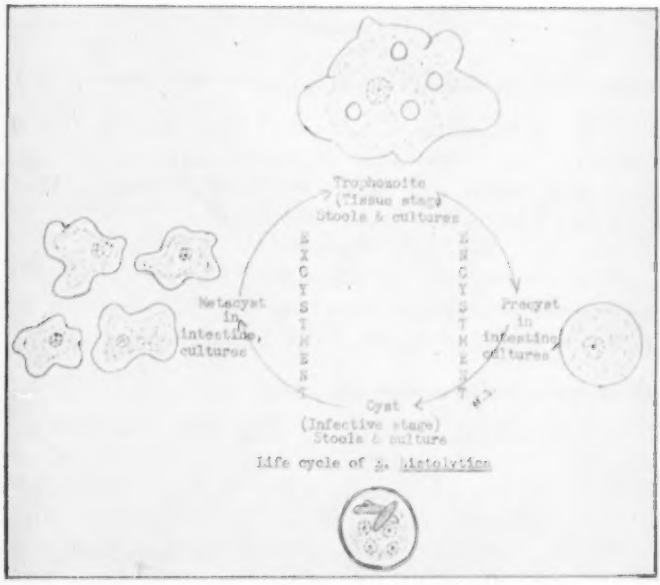

Fig. 1. **The life cycle of *Endameba histolytica*.**

No castor oil, mineral oil, or barium should be given to the patient if the stools are going to be examined for amebas. The chances of finding the ameba in the stools can be increased by giving a mild saline purgative (sodium sulfate) or saline enema.

Freshly passed stools should be examined for motile trophozoites. If this is not feasible, the stools should be kept in the incubator until they are examined. The trophozoites should be distinguished from macrophage cells, and cysts and precysts from leukocytes.

Zinc Sulfate Centrifugal Flotation[5]

1. Suspend feces 1 to 10 parts in tap water and filter through wet cheese cloth, and put about 10 cc. in a Wassermann tube.
2. Centrifuge for 45–60 seconds at 2500 rpm, decant the supernatant, resuspend in water to fill the tube. Repeat 2 or 3 times, until the fluid is clear.
3. Decant fluid and resuspend in zinc sulfate solution (sp. gr. 1.18 and 33%) and centrifuge for 45–60 seconds.
4. Remove several loopfuls of the floating surface material or film and add to a drop of Lugol's iodine on a slide and examine under the low- and high-power lenses of the microscope.

Formalin-Ether Sedimentation[12]

1. Centrifuge 10 cc. saline suspension of feces, filtered through wet cheese cloth, 3 to 4 times until the supernatant is clear.
2. Decant supernatant and replace with 10% Formalin. Mix thoroughly and set test tube aside for 5 minutes.
3. Add 3 cc. ether and shake vigorously.
4. Centrifuge at relatively low speed for 2 minutes. There will be a small amount of sediment containing the cysts and ova, a layer of formalin, a plug of debris, and a surface layer of ether.

Preservation of Trophozoites

For the preservation of the motile stage of amebas in the stools, PVP fixative (polyvinyl alcohol) is very useful, but the cysts and ova become distorted. The addition of PVP to the liquid stools, and stools produced by purgation results in making satisfactory permanent slides for staining with the iron hematoxylin method. Feces preserved in PVP is suitable for staining for several months, and easy to ship. The stools are mixed in 3 or more parts of the fixative which has the following formula:

Dissolve at 75° C.

Powdered PVP	5.0 Gm.
Glycerol	1.5 cc.
Glacial acetic acid	5.0 cc.
Saturated $HgCl_2$ solution in water	93.5 cc.

Culture of Amebas

Endameba histolytica can be cultured from the stools and pus, but is not practical for diagnostic purposes. In cultures, they feed on rice starch and bacteria. Encystment occurs in 18 to 24 hours. Boeck Drbohlav egg medium with buffered saline overlay containing sterile rice starch, penicillin and streptomycin is commonly used. The cysts can be concentrated, washed free of zinc sulfate, or the fresh specimen can be used for inoculating the medium. Subcultures should be made every 48 hours otherwise the amebas cannot survive. Balamuth and Nelson medium can also be used. Shaeffer Frye medium yields practically sterile cultures, but the growth of amebas is scanty. Cultures of amebas with a single organism (Reece) such as organism *t*, *Clostridium perfringens*, *Escherichia coli* or with *Trypanosoma cruzi* (Phillips) are

used for experimental studies. The addition of carbomycin to the standard bacteria ameba cultures prolongs the life of the amebas.

Animal Inoculation

Kittens, dogs, and monkeys are very susceptible to amebiasis, and guinea pigs, pigs, rabbits, rats, and mice can also be used in the study of experimental amebiasis, but are not practical in the laboratory diagnosis of amebiasis.

Complement Fixation

The Craig complement-fixation test is of diagnostic value in hepatic amebiasis when the stools and pus from the abscess are negative for ameba. It is also positive in intestinal amebiasis. Complement-fixing antibodies are lost when the patient is cured of amebiasis. A commercial antigen (prepared by Hynson, Westcott, and Dunning of Baltimore, Md.) can be used. In the laboratory, antigen can be prepared by extracting the cultures with alcohol,[4] from cultures grown with organism *t* (N I H), material containing amebas obtained from the bowel of dogs (Craig-Scott), or from cysts obtained from cultures freed of bacteria (Stone). At the present, the serologic diagnosis of amebiasis is in a state of flux. There is no standard antigen. The antigenic material also contains bacterial fractions which may give anticomplementary reactions or false positives. A standard test will be available only when large numbers of amebas can be cultured free of bacterial contamination.

Sigmoidoscopic Examination

The night before the examination the patient should be given a mild saline purgative. The next morning, saline enemas should be given to clean the colon. The examination may be completely negative if there are no lesions within the reach of the scope. In a series of 300 patients, 211 were positive by this method. The lesions may be very mild in the form of isolated small hemorrhagic spots with intervening normal mucosa. Scattered pinhead-sized ulcers surrounded by erythematous reaction, shallow ulcers containing mucus, and necrotic material with irregular outline, undermined, congested, and heaped-up edges are observed in most cases. In severe cases, the entire mucosa may be covered with lesions of various sizes and shapes containing purulent mucus, necrotic material, and oozing blood. Microscopic examination

may show motile trophozoites. In shigellosis, the entire mucosa is inflamed and ulcerated without any normal mucosa. In ulcerative colitis, the ulceration is very extensive and the tissues are very friable, and there is a good deal of bleeding due to instrumentation.

X-ray Diagnosis

Cecal lesions are visible in 1 in 4 cases of amebiasis. The wall of the cecum or rectum and sigmoid may be thickened, irregular, granular, and spastic, and the outline shaggy with narrowed lumen. The cecum is conical, the ileocecal valve abnormally patent, with cecal and appendicular deformity or a filling defect. Amebomas with the appearance of filling defects may be mistaken for carcinoma. Other diseases or conditions of the bowel may simulate the roentgenologic signs of intestinal amebiasis. In hepatic amebiasis, hepatomegaly is a common finding. Amebic abscess of the liver is characterized by elevation, tenting, and fixation of the right half of the diaphragm.

Miscellaneous Findings

The erythrocyte sedimentation rate is increased, and the blood picture shows hypochromic microcytic anemia and, with amebic abscess of the liver, leukocytosis. Liver-function tests may be normal, or there may be delayed excretion of bromsulfalein, and positive cephalin flocculation. Stools may contain Charcot-Leyden crystals, increased numbers of normal intestinal bacteria, and increased frequency of *Streptococcus fecalis*.

DIFFERENTIAL DIAGNOSIS

There should be no difficulty in making the correct diagnosis of amebiasis if the following are kept in mind:

1. Be amebiasis-conscious because its distribution is universal.
2. Take a detailed and thorough clinical history, particularly concerning the gastrointestinal tract, vague and indefinite symptoms, and exposure to infection during sojourns in hyperendemic areas.
3. Look for hepatomegaly and palpable or thickened cecum and sigmoid.
4. Perform stool examinations, including concentration methods and purgative specimens.
5. Perform a sigmoidoscopic examination.
6. Look for X-ray evidence of intestinal and hepatic amebiasis.
7. Make therapeutic tests.

Conditions Causing Diarrhea

In acute amebiasis where diarrhea or dysentery is the clinical manifestation, any condition or disease which gives rise to these symptoms should be considered in the differential diagnosis such as shigellosis (Table 1), ulcerative colitis, regional enteritis, cholera, salmonellosis, staphylococcic food poisoning (gastroenteric toxin), superinfection with staphyloccocus during antibiotic therapy, acute febrile and exanthematous fevers, balantidiasis, trichinosis, pernicious malaria, mercury and arsenic poisoning, and so on. Chronic conditions or diseases which give rise to diarrhea or dysentery include chronic ulcerative colitis, ileitis, hyperthyroidism, digitalis toxicity, chronic arsenic and mercury poisoning, pernicious anemia, carcinoma or lymphosarcoma of the bowel, uremia, amyloid disease, leukemia, cystic disease of the pancreas, celiac disease, sprue, steatorrhea, pellagra, tubercular enteritis, visceral leishmaniasis, schistosomiasis, hookworm disease, food allergies, and emotional factors.

TABLE 1. Differential Diagnosis of Amebiasis and Shigellosis

	Amebiasis	Shigellosis
Onset	Usually insidious	Acute
Incubation	Indefinite period	Under 1 week
Distribution	Endemic but may become epidemic	Epidemic but may become endemic
Incidence in children	Acute form rare	More frequent
Constitutional symptoms	Rare except in very severe cases and in amebic abscess of the liver	Marked, especially in Shiga dysentery; e.g., dehydration, toxemia, fever, leukocytosis, general malaise
Pain	Local pain and tenderness over cecum and sigmoid	General pain and tenderness all over abdomen
Complication	Hepatic abscess formation	Polyarthritis
Stools	Small and copious, containing necrotic cells, mucus, macrophages, few polys, Charcot-Leyden crystals, bacteria, *E. histolytica*, erythrocytes.	Frequent and scant, with pus cells, erythrocytes, few bacteria, and *Shigella*.
Ulcers	Crateriform, bottle neck, undermined heaped-up edges, normal intervening mucosa; mainly in cecum and sigmoid and rectum	Diffuse superficial ulceration, inflammation, and necrosis of mucosa
Blood serum	Complement-fixation test positive in 90% of cases	Agglutination of *Shigella*
Therapeutic tests	*Intestinal amebiasis:* tetracycline and fumagillin *Hepatic amebiasis:* chloroquin and/or emetine	Tetracycline and sulfadiazine; Shiga antitoxin in Shiga dysentery.

Conditions Causing Constipation

In chronic amebiasis where the main finding is chronic constipation, the following should be considered in the differential diagnosis: spastic or atonic colon, emotional and mental diseases or disturbances, tumors of the bowel, megacolon, fistulas or fissures in ano, genitourinary tract diseases, fecal impaction, diseases of the central nervous system (general paralysis, tabes), diabetes, diverticula, improper diet, and postoperative adhesions.

Conditions Causing Liver Abscess

Amebic abscess of the liver should be differentiated from subdiaphragmatic abscess, septicemia and bacteremia, acute malaria, Hodgkin's disease, suppurative cholangitis, acute cholecystitis, right-chest empyema or right-lower-lobe pneumonia, biliary cirrhosis, acute myeloid leukemia, primary tumors of the liver, Banti's syndrome, and infected hydatid cyst.

TREATMENT

An ideal amebicide is a drug which is active in vitro and in vivo against the cysts and trophozoites of *E. histolytica*, is nontoxic, concentrates at the site of the pathology (colon and/or liver), and is reasonably cheap. As of the writing of this paper, no such drug fulfills all these criteria, and there will always be a keen interest in improving the therapy of amebiasis. Since hepatic amebiasis is a complication or extension of the intestinal phase, adequate therapy should also include the treatment of the intestinal stage. In intestinal amebiasis, adequate measures should be taken to prevent the hepatic complication.

Antibiotic Drugs in Intestinal Amebiasis (Table 2)

Tetracycline drugs are available in 0.25-Gm. capsules or tablets. The recommended dose is 2 Gm. daily for 10 days, given in 3 daily doses after meals. It is also effective in 0.5-Gm. doses 3 times daily for 10 days, or 2 Gm. daily for 7 days. The tetracycline group exerts both amebicidal and bacteriostatic effect on the amebic lesions, thus controls also the secondary bacterial infection or inflammation. In vitro studies indicate that *E. histolytica* develops resistance to chlortetracycline (Watt and Vandegrift) and oxytetracycline (Seneca and Murphy).

Fumagillin is also very effective. In vitro tests indicate that it is highly amebicidal (1:100 million concentration), but has no antibac-

TABLE 2. Antibiotics in Intestinal Amebiasis

Antibiotic	Author	Date	No. patients	No. failures	% Failures
Oxytetracycline	Frye and McHardy	1954	435	37	
	Sappenfield *et al.*	1955	338	20	
TOTAL			773	57	7.3
Chlortetracycline	Frye and McHardy	1954	697	116	16.6
Tetracycline	Seneca	1955	20	1	5.0
Chloramphenicol	Frye and McHardy	1954	72	53	73.6
Bacitracin	Frye and McHardy	1954	205	65	31.2
Neomycin	Frye and McHardy	1954	22	14	66.6
Fumagillin	Frye and McHardy	1954	119	28	
	Sappenfield *et al.*	1955	356	22	
	Anderson *et al.*	1954	14	6	
	Anderson *et al.*	1955	10	2	
			499	58	11.6
Carbomycin	Sodeman	1953	4	0	
	Seneca	1954	17	1	
			21	1	4.7
Erythromycin	Anderson *et al.*	1954	17	2	
	Nelson *et al.*	1954	76	4	
	Villarejos	1955	64	2	
			157	8	5.1
Nystatin[a]	Seneca	1956	5	0	
Novobiocin[a]	Seneca	1956	7	0	
Erythromycin + fumagillin	Anderson *et al.*	1954	21	5	23.7
Nystatin + tetracycline[a]	Seneca	1956	9	0	
Nystatin + tetracycline + novobiocin[a]	Seneca	1956	7	0	

[a] Studies in progress.

terial properties. It comes in 10 mg. capsules, and is used in 10- to 20-mg. doses 3 times daily for 10 to 14 days.

Carbomycin and erythromycin are supplied in 100- and 250-mg. tablets or capsules. They are recommended in one to two gram daily doses for 1 week to 10 days. Erythromycin stearate in hepatic amebiasis has given very encouraging results.

Neomycin, bacitracin, and chloramphenicol have been used to a limited extent. Recently nystatin, novobiocin, and combination of antibiotics are being used with promising results.

Toxic Side Effects

The toxic side effects of tetracycline drugs include nausea, vomiting, diarrhea, and perianal pruritus. Gastric irritation can be avoided by giving the drugs after meals, with milk, cultured buttermilk, or yogurt.

If the diarrhea continues, the drug should be discontinued. For pruritus, hydrocortisone ointment should be applied locally. The serious and at times dangerous side effects include enterocolitis and pseudomembranous or diphtheritic enteritis or enterocolitis. These are the result of superinfection with *Micrococcus pyogenes aureus*, *Pseudomonas aeruginosa*, or *Proteus*. With severe diarrhea and vomiting, the patient loses fluids and electrolytes, may have bloody stools, perforation with peritonitis, pyrexia, and oliguria, elevation of blood urea and loss of sodium and chlorides, low blood pressure, collapse, coma, which may terminate in death. Stools should be cultured for staphylococcus in blood medium as well as the usual media for coli-aerogenes-*salmonella-shigella*. The medication should be stopped immediately, fluid and electrolytes should be administered, and sulfadiazine, erythromycin, carbomycin, novobiocin (if the organisms are sensitive to these antibiotics) be given to combat the superinfection. Vitamins and yogurt may also help, but the essential feature of the therapy is symptomatic treatment of toxic shock. It may be necessary to resort to ACTH and oxysteroids. European writers refer to this condition as the "choleriform syndrome." Overgrowth of *Candida albicans* may also lead to serious complications. It should also be treated symptomatically, and nystatin is considered to be a specific drug against this fungus.

The toxic side effects of fumagillin are vertigo, anorexia, dermatitis, nausea, vomiting, abdominal cramps, diarrhea, desquamation of the skin on the hands, pruritus, leukopenia and even depression of the bone marrow, although aplastic anemia has not been observed.

Halogenated Hydroxyquinolines

Diodoquin (60.5 to 64% iodine), or 5,7-diiodo-8-hydroxyquinoline, is supplied in 0.21-Gm. tablets. It is prescribed in 2 or 3 tablets, 3 times daily for 10 to 20 days. Following the ingestion, the blood levels range 45.6 to 437.25 μg./100 cc. Chiniofon (Yatren) (26.5 to 29% iodine) is iodoxyquinoline sulfonic acid and is used specifically in cyst carriers. It is supplied in 0.25-Gm. tablets and is used in doses of 0.75 to 1 Gm. 3 times daily for eight to ten days. Following its ingestion, 12.9 per cent is absorbed, and 7.4 per cent is excreted in the urine. Vioform (38 to 41% iodine and 11.2 to 12.2% chlorine) is iodochlorhydroxyquinoline. It is supplied in 0.25-Gm. capsules, and is used in a one-capsule dose, 3 times daily for 10 days, repeated after an interval of 1 week. It is the most readily absorbed member of this group, giving the peak blood level on the seventh day of 10 days treatment period.

The side effects of these compounds are very few. Diodoquin has the least side effects, giving rise to an occasional headache. Chiniofon causes diarrhea, and Vioform may cause nausea, diarrhea, palpitation, dyspnea, headache, and abdominal colic.

Arsenicals

Pentavalent arsenicals were commonly used in the treatment of amebiasis in the past. Carbarsone (28.5% arsenic) is 4-carbaminophenylarsonic acid. It is supplied in 0.25-Gm. capsules and is used in two daily doses of 0.25-Gm. for ten days, and repeated after an interval of 2 weeks. Acetarsone, Treparsol, and Milibis (bismuth glycolylarsanilate) have also been used, but are inferior to carbarsone. They are potentially toxic because arsenic can be absorbed and give rise to toxic symptoms. For example, 2 per cent of Milibis is excreted in the urine. The trivalent arsenicals are more potent amebicidal agents, but they are also more toxic. The substitution of SH for oxygen produces thioarsenites (thiocarbarsone) which are less toxic and more potent than the pentavalent members and are effective in 90 per cent of the patients. Additional investigations are in progress. Recently arsthinol (Balarsen) was introduced for the therapy of amebiasis (Levy and Talley, 1952; Most *et al.* 1954). It has been used in 4 to 22 mg./kg. for 5 days in 192 children and adults who had mild to asymptomatic amebiasis, with an apparent definitive elimination of *E. histolytica* in 88 per cent of cases.

Antibiotic Drugs in Hepatic Amebiasis (Table 3)

Antibiotic therapy in hepatic amebiasis is a novelty. Erythromycin alone or in combination with fumagillin has given fairly satisfactory results. Additional investigation with the newer antibiotics which give rise to high blood and liver levels may give better results. Novobio-

TABLE 3. Antibiotics in Hepatic Amebiasis

Antibiotic	Author	Date	No. patients	No. failures
Erythromycin stearate	Anderson *et al.*	1955	15	1
	Nelson *et al.*	1955	28	8
Fumagillin	Anderson *et al.*	1955	11	8
Erythromycin stearate	Anderson *et al.*	1955	19	5
Fumagillin	Nelson *et al.*	1955	1	0
TOTAL			74	22 (29.7%)

cin (Albamycin or Cathomycin), is amebicidal, has a bacterial spectrum which is similar to erythromycin and gives rise to very high blood levels. It should be tried in hepatic amebiasis.

Chloroquin (Arlen) is the drug of choice in amebic hepatitis or abscess. It is recommended in a 0.3-Gm. oral dose, 3 times daily for 2 days, followed by 0.3 Gm. daily for 12 to 19 days. On this therapy, the blood level is about 15 μg./100 cc. It is well tolerated, but occasionally it may give rise to gastric irritation. If there is no therapeutic response, the dose should be repeated or the amount may be doubled, or supplemented with emetine hydrochloride injections of 0.065 Gm. daily subcutaneously, not exceeding 6 doses. Surgical drainage by aspiration should be done if the abscess is large.

Emetine has no effect on the cyst stage; therefore, its specificity is in acute amebic dysentery and hepatic amebiasis. Its toxicity is such that it should be used only if other measures fail. It is curative in a third of the cases, symptomatically improves a second third, and has no effect in the remaining third. The highest concentration of the drug is in the lungs, followed in order by the kidneys, spleen, liver, heart, lymph nodes, colon, striated muscle, and brain. It is retained in the spleen for 42 days. It is extremely toxic to the heart muscle, causing hypotension, tachycardia, precordial pain, dyspnea, inversion of T wave, prolongation of A-V conduction (QT and PR intervals), widening of the ventricular complex, and arrhythmia. The neuromuscular symptoms include aching and stiffness of the muscles, fatigability, tremors, and edema and cellular degeneration of the skeletal muscles; neuritis is rare. The gastrointestinal symptoms include nausea, vomiting, diarrhea, abdominal cramps, blood and mucus in the stools, dizziness, and faintness. Occasionally there is pain and tenderness at the site of the injection, eczema, and urticaria. Emetine is contraindicated in the presence of heart diseases and pregnancy, and in children it should be used very cautiously.

Symptomatic Treatment

There may be nutritional disturbances, avitaminosis, and hepatic dysfunction in patients who are chronically infested with *E. histolytica*. The patient should be put on a high-carbohydrate, high-protein, high-vitamin diet. Parenteral injections of Vitamin B_{12}, 500 to 1000 μg. dose two to three times a week, are helpful. Iron and liver extract may be indicated for anemia. In case of secondary bacterial complications, penicillin plus streptomycin, tetracycline, or sulfadiazine

should be given. Travelers or temporary residents in the tropics should leave for home if amebic hepatitis or abscess is apparent, and should not return to endemic areas.

DIENTAMEBIASIS

For many years, there has been some question of the possibility of *Dientameba fragilis* as an intestinal pathogen. The patients infested with this pathogen exhibit symptoms which subside following antiamebic treatment. In an examination of 1130 appendixes, 15 or 1.3 per cent, had *D. fragilis*. This is about twice the incidence found in routine stool examinations. In children and adults this condition may be associated with nausea, vomiting, slight fever, diarrhea, and abdominal pain. *D. fragilis* resembles *E. histolytica* in that both ingest red blood cells, but it does not have the invasive powers of the tissues of the latter. The appendixes from cases of dientamebiasis exhibit acute suppurative reaction, characterized by lymphoid hyperplasia, fibrosis of the submucosa due to the prolonged low-grade irritant effect, with minimal injury and inflammatory reaction which finally results in increased fibrous connective tissue.[16]

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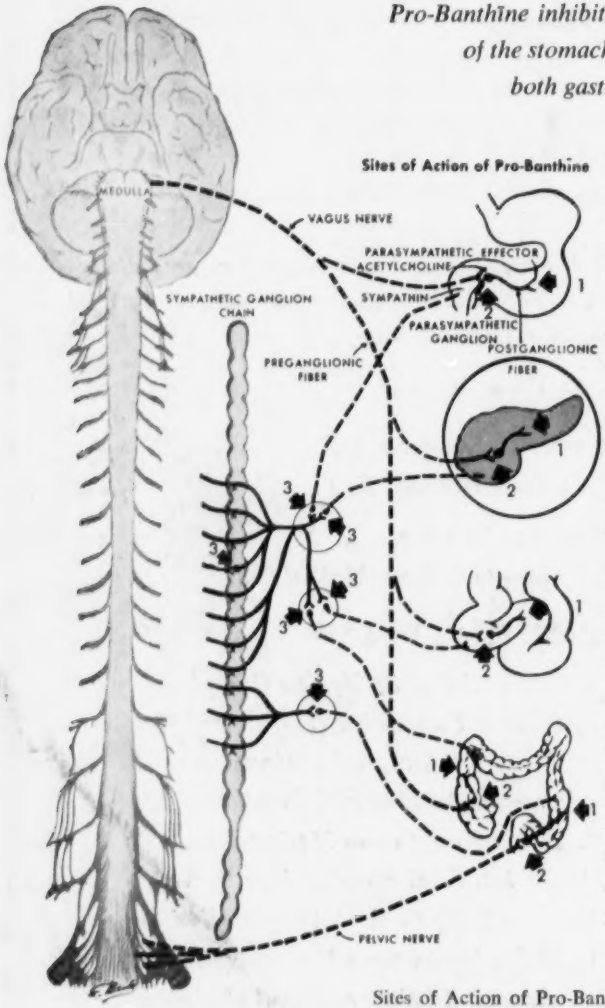

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